Well-conducted randomized clinical trials (RCT) are essential for the objective assessment of the value of new diagnostic or therapeutic medical interventions. They also will give us information about the effect of the intervention on cost and quality of life. Although the RCT was introduced >50 years ago, the requirements to ensure the best possible quality are continuously scrutinized.1–4 That holds for several aspects of the RCT, such as the proper selection of patients, fulfilling strict criteria to make groups comparable, correct calculation of the required number of patients, well-defined end points, adequate information and follow-up care of the patients, and clarity about medicolegal aspects. An important issue in the RCT is the required length of the study to come to a meaningful outcome.

In the present issue, data are reported5 on a subset of a 120 patients who participated in the Canadian Implantable Defibrillator Study (CIDS)6 and continued with the treatment assigned to them after CIDS was formally ended.

CIDS was a RCT comparing the effect of implantation of a defibrillator with the administration of amiodarone in patients needing secondary prevention of sudden cardiac death after having survived an episode of ventricular fibrillation or poorly tolerated ventricular tachycardia. At the end of CIDS, no statistically significant difference in risk reduction in overall mortality was found between the implantable cardioverter defibrillator (ICD) and the amiodarone arm, and the CIDS steering committee made no formal recommendation regarding ongoing management of the patients receiving amiodarone.

Although a meta-analysis of CIDS combined with two other secondary prevention studies [AVID (Antiarrhythmic vs Implantable Defibrillator)7 and CASH (Cardiac Arrest Study Hamburg)]8 demonstrated a significant reduction in death from any cause with the ICD,9 the CIDS investigators from one center decided to ask their patients, after informing them about the CIDS results, to remain on the assigned therapy unless adverse affects occurred. All 120 patients from that center agreed, and apparently the institutional review board also agreed. One might argue about the ethical acceptability of the decision to continue the study in view of the results of the meta-analysis.9 It is possible that in that decision making the investigators looked at the findings of the AVID study showing that the ICD contributed 2.3 months of added survival at a cost of around US$125.00 for 1 life-year saved. After extending the duration of the follow-up with a mean of 5.6±2.6 years, the study showed a significantly higher all-cause mortality in the amiodarone group, which could be explained by the difference in arrhythmic deaths. Another important finding was the high incidence of side effects related to amiodarone (82% of patients) necessitating discontinuation of the drug in 26%. Although a relatively low percentage of patients in the amiodarone group received a β-blocker and an angiotensin-converting enzyme inhibitor, the outcome of the study reinforces the value of an ICD implant for the secondary prevention of arrhythmic cardiac death and questions the value of amiodarone treatment in patients with a previous life-threatening ventricular arrhythmia and diminished left ventricular function. In the study by Bokhari et al.,5 no data are given about the health economic consequences of the side effects of amiodarone therapy.

Each time a RCT is planned, the question of how long the study should last comes up. This obviously depends on the type of patient studied and the intervention that is going to be evaluated.

The study reported in the present issue of Circulation® is an example of the possibility of a delayed effect of an intervention, in this case increasing side effects of amiodarone over time. It is well known that the incidence of side effects of amiodarone increases with the duration of its administration and the height of the dose.10 The patients reported by Bokhari et al5 received a daily dose of amiodarone slightly above 300 mg for many years. This resulted in increasing superiority of the ICD arm over time.

Delayed effects can play an important role in studies in which patients are randomized to invasive versus noninvasive therapy. The invasive arm may initially have increased morbidity and even increased mortality because of the invasive procedure. This can be shown by comparing events during the hospital period in the invasive and the noninvasive arms. However, after discharge, the survival curves may diverge in favor of invasive therapy. Such a situation may occur in studies in heart failure patients of whom half are randomized to resynchronization of ventricular activation by biventricular or left ventricular pacing.11 Improvement in cardiac function may take awhile after the resynchronization procedure, and the RCT should therefore last long enough for researchers to become informed about the true value of that therapy.
Delayed effects may also occur in studies in which other types of invasive therapy (catheter ablation of arrhythmias, surgical interventions) are compared with drug therapy.

Positive delayed effects are not necessarily typical for the invasive arm.

In prevention studies of sudden death in patients with poor left ventricular function comparing ICD versus no device therapy, the initial beneficial effect of the ICD on overall mortality might possibly disappear over time because of cardiac damage from defibrillation shocks leading to increased mortality from worsening of heart failure.

In every RCT, the possibility of a delayed effect should therefore be considered in relation to the type of patient and the therapies studied.

The length of the RCT also plays an important role in determining health economic aspects of a new intervention, especially when an expensive device or surgical procedure is compared with drug therapy. Better cost efficacy of the ICD implant for primary prevention of sudden cardiac death in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) I and the Multicenter Unsustained Tachycardia Trial (MUST) versus MADIT II was not only based on the selection of patients (inducibility of a sustained ventricular tachycardias in MADIT I and MUST) but also on the longer follow-up period in MADIT I and MUST. A sufficiently long duration of follow-up is also important in studies dealing with less life-threatening situations, such as in a comparison between catheter ablation of the tachycardia mechanism and antiarrhythmic drug therapy in patients with supraventricular tachycardias, atrial flutter, and atrial fibrillation. It will take time before an expensive invasive treatment becomes cost effective when compared with antiarrhythmic drug treatment for which costs are determined by arrhythmia recurrences and side effects of drugs.

An important role in determining the length of the RCT is played by the Data and Safety Monitoring Board (DSMB), also during the study. Paradoxically, although blinded for the type of treatment assigned to the different study arms, the DSMB should have an open eye for the events occurring during the study. The DSMB should carefully follow the curves illustrating end points to identify the possibility of delayed effects because that may lead to the advice of a longer duration of the RCT than originally planned.

References

Key Words: Editorials ▪ arrhythmia ▪ defibrillation ▪ trials
Randomized Clinical Trials: How Long Should They Last?
Hein J. Wellens

doi: 10.1161/01.CIR.0000134919.98104.22

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/110/2/107

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/